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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/806,477	03/23/2004	Jeffrey A. Engler		1697

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EXAMINER	
BALLARD, KIMBERLY A	
ART UNIT	**PAPER NUMBER**
1649	

MAIL DATE	DELIVERY MODE
08/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,477	ENGLER ET AL.	
	Examiner	Art Unit	
	Kimberly A. Ballard	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendments

Claims 1-7 have been amended as requested in the response filed June 1, 2007. Claims **1-7** are pending and under examination in the instant office action.

Formal Matters

It is noted that the current claims submitted June 1, 2007, although correctly identified as "Currently Amended", have been underlined in their entirety, wherein portions of the text not newly added have also been underlined. Applicants' attention is directed to MPEP § 714 (c)(2) regarding amendments to claims, which states:

> *When claim text with markings is required.* All claims being currently amended in an amendment paper shall be presented in the claim listing, indicate a status of "currently amended, " and be submitted with markings to indicate the changes that have been made **relative to the immediate prior version of the claims** (emphasis added). The text of any added subject matter must be shown by underlining the added text. The text of any deleted matter must be shown by strike-through except that double brackets placed before and after the deleted characters may be used to show deletion of five or fewer consecutive characters. The text of any deleted subject matter must be shown by being placed within double brackets if strike-through cannot be easily perceived. Only claims having the status of "currently amended, " or "withdrawn " if also being amended, shall

include markings. If a withdrawn claim is currently amended, its status in the claim listing may be identified as "withdrawn — currently amended. "

Oath/Declaration

The corrected oath/declaration filed June 1, 2007 is acknowledged and made of record.

Maintained and New Claim Rejections, Necessitated by Amendment

Claim Objections

Claim 1, as amended, is objected to because of the following informalities: the claim contains what appear to be inadvertent typographical errors. For example, line 2 recites "purified peptide **is** binds the transferrin**g** receptor...." (bolded emphasis added), wherein the word "is" and the "g" on transferrin are unnecessary. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The rejection of claims 1, 2 and 6 under 35 U.S.C. 102(a) as being anticipated by WO 00/25814 by Charalambous et al. (published May 11, 2000) is maintained for reasons of record.

In the response filed June 1, 2007, Applicants argue that Charalambous does not teach or suggest a peptide that is capable of binding to the transferrin receptor without disrupting the ability of the transferrin receptor to bind transferrin. Moreover, Applicants assert that one of ordinary skill in the art would not be able to predict that the claimed peptide fused with another protein, peptide, chemotherapeutic agent or imaging agent would be effective for delivering such secondary molecules.

Applicant's arguments filed June 1, 2007 have been fully considered but they are not persuasive. The peptide taught by Charalambous et al. and the peptide comprising the amino acid sequence of SEQ ID NO: 1 (HAIYPRH) of the instantly claimed invention are identical, as indicated by their identical amino acid sequences indicated below:

```
  Query Match             100.0%;  Score 43;  DB 3;  Length 7;
  Best Local Similarity   100.0%;  Pred. No. 2.1e+06;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 HAIYPRH 7  (SEQ ID NO: 1 of the instant application)
              |||||||
Db          1 HAIYPRH 7  (Charalambous et al. WO 00/25814)
```

That Charalambous did not recognize that the peptide could bind to the transferrin receptor without interfering with the receptor's functioning is irrelevant because the heptapeptide taught by Charalambous, and those peptides linked to a carrier protein, would inherently possess ability to bind to the transferrin receptor as instantly claimed. Further, it is noted that "[p]roducts of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke*. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459

F.2d 531, 173 USPQ 685 (1972).. Thus, the claimed invention, as a whole, is clearly anticipated in the absence of evidence to the contrary.

The rejection of claims 1-2 and 6-7 under 35 U.S.C. 102(b) as being anticipated by WO 98/53804 by Smith et al. (published December 3, 1998) is maintained for reasons of record.

In the response filed June 1, 2007, Applicants argue that Smith does not teach or suggest a peptide that is capable of binding to the transferrin receptor without disrupting the ability of the transferrin receptor to bind transferrin. Moreover, Applicants assert that one of ordinary skill in the art would not be able to predict that the claimed peptide fused with another protein, peptide, chemotherapeutic agent or imaging agent would be effective for delivering such secondary molecules.

Applicant's arguments filed June 1, 2007 have been fully considered but they are not persuasive. The peptide taught by Smith et al. and the peptide comprising the amino acid sequence of SEQ ID NO: 1 (HAIYPRH) of the instantly claimed invention are identical, as indicated by their identical amino acid sequences indicated below:

```
Query Match             100.0%;  Score 43;  DB 2;  Length 7;
  Best Local Similarity   100.0%;  Pred. No. 2.1e+06;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 HAIYPRH 7  (SEQ ID NO: 1 of the instant application)
              |||||||
Db          1 HAIYPRH 7  (Smith et al. WO 98/53804)
```

That Smith did not recognize that the peptide could bind to the transferrin receptor without interfering with the receptor's functioning is irrelevant because the HAIYPRH

peptide taught by Smith would inherently possess ability to bind to the transferrin receptor as instantly claimed. Additionally, Smith discloses that the peptides can be used to target genes, proteins, pharmaceuticals, or other compounds to particular muscle tissue by ligating the muscle-specific peptide to pharmaceuticals, chemotherapeutic agents, proteins and nucleic acids (see p. 7, lines 3-4, claims 9-10 and 27, and p. 10, lines 7-11), thus meeting a newly amended limitation of claim 2. Because all proteins comprise antigenic sequences, the recited limitation of an "antigen" of claim 6 would also be met. Further, it is noted that "[p]roducts of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke*. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Thus, the claimed invention, as a whole, is clearly anticipated in the absence of evidence to the contrary.

The rejection of claims 1-2 and 7 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,201,104 B1 to MacDonald et al. (issued March 13, 2001, filed December 4, 1998) is maintained for reasons of record.

In the response filed June 1, 2007, Applicants argue that MacDonald does not teach or suggest a peptide that is capable of binding to the transferrin receptor without disrupting the ability of the transferrin receptor to bind transferrin. Moreover, Applicants assert that one of ordinary skill in the art would not be able to predict that the claimed peptide fused with another protein, peptide, chemotherapeutic agent or imaging agent would be effective for delivering such secondary molecules.

Applicant's arguments filed June 1, 2007 have been fully considered but they are not persuasive. The peptide taught by MacDonald (SEQ ID NO: 7) comprises the instantly claimed amino acid sequence HAIYPRH (SEQ ID NO: 1) attached to GGGS, which is a flexible linker used, for example, for attaching the hepapeptide HAIYPRH to another protein or agent. The sequence alignment for the two amino acid sequences is indicated below:

```
Query Match             100.0%;  Score 43;  DB 3;  Length 7;
  Best Local Similarity   100.0%;  Pred. No. 2.1e+06;
  Matches    7;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;

Qy          1 HAIYPRH 7
              |||||||
Db          1 HAIYPRH 7
```

That MacDonald did not recognize that the peptide could bind to the transferrin receptor without interfering with the receptor's functioning is irrelevant because the HAIYPRH peptide taught by MacDonald would inherently possess ability to bind to the transferrin receptor as instantly claimed. Compositions comprising peptides such as HAIYPRH that bind ANGIOSTATIN™ protein and/or ENDOSTATIN™ protein are disclosed by MacDonald to be capable of being linked to a cytotoxic agent and used for treating or repressing the growth of a cancer, thus anticipating the "chemotherapeutic agent" of amended claim 2. MacDonald also teaches the HAIYPRH can be labeled with other suitable molecules or proteins, and can be used in compositions for the detection and visualization (*in vivo* and *in vitro*) of angiogenesis-related protein binding sites with techniques including, but not limited to, positron emission tomography, autoradiography, flow cytometry, radioreceptor binding assays, and immunohistochemistry (see column 7, lines 55-62 and column 8, lines 40-43). Accordingly these teachings would meet the limitation of an "imaging agent" recited in amended instant claim 2. MacDonald further discloses nucleotide sequences encoding the HAIYPRH peptide, as well as expression vectors containing the nucleotide sequences (see column 7, lines 31-42) and compositions comprising these expression vectors (see column 11, lines 39-51), thus anticipating instant claim 7. Further, it is noted that "[p]roducts of identical chemical composition can not have mutually exclusive properties." A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Where, as here,

the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See *In re Ludtke*. Whether the rejection is based on "inherency" under 35 USC 102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Thus, claimed invention of claims 1-2 and 7 is clearly anticipated in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 4 and 5, as amended, under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,201,104 B1 to MacDonald et al., in view of Hazum et al. (*Proc Natl Acad Sci USA*, 1980; 77(11): 6692-6695) and Tarasova et al. (*J Biol Chem*, 1997; 272(23): 14817-14824) is maintained for reasons of record and is further applied to amended claim 4.

The claims are drawn to a composition comprising a purified peptide containing the sequence HAIYPRH (SEQ ID NO: 1), wherein said peptide is fused to an imaging agent, wherein said imaging agent is a fluorescing agent (claim 4), and wherein said fluorescing agent is green fluorescent protein (claim 5).

In the response filed June 1, 2007, Applicants argue that MacDonald does not teach or suggest a peptide that is capable of binding to the transferrin receptor without disrupting the ability of the transferrin receptor to bind transferrin. Applicants further

assert that neither Harzum nor Tarasova teach or suggest a peptide that is capable of binding to the transferrin receptor without disrupting the receptor's functioning, and that one of ordinary skill in the art would not be able to predict that the claimed peptide fused with another protein, peptide, chemotherapeutic agent or imaging agent would be effective for delivering such secondary molecules.

Applicant's arguments filed June 1, 2007 have been fully considered but they are not persuasive. As discussed above, the peptide and compositions taught by MacDonald (SEQ ID NO: 7) comprise the instantly claimed amino acid sequence HAIYPRH (SEQ ID NO: 1) attached to GGGS, which is a flexible linker used, for example, for attaching the hepapeptide HAIYPRH to another protein or agent. That MacDonald, Harzum or Tarasova did not recognize that the peptide could bind to the transferrin receptor without interfering with the receptor's functioning is irrelevant because the HAIYPRH peptide taught by MacDonald would inherently possess ability to bind to the transferrin receptor as instantly claimed. Hazum and Tarasova teach the production and use of fluorescently-labeled peptides and proteins for visualization techniques. For example, Tarasova teaches a chimeric protein consisting of the cholecystokinin receptor type A (CCKAR) fused to green fluorescent protein (GFP) for studying receptor localization, internalization, and recycling in live cells in real time (see p. 14817), thus addressing a limitation of instant claim 5.

One of skill in the art at the time the invention was made would readily know that in order to perform some of these detection and/or visualization techniques, in particular flow cytometry or immunohistochemistry, it is necessary and/or convenient to attach a

fluorescent label to the binding peptide. For example, fluorescently labeled peptides are routinely used for visualization techniques as evidenced by Hazum et al. and Tarasova et al. The skilled artisan therefore would be motivated to make and use fluorescently-labeled binding proteins for visualizing and quantitating sites of ANGIOSTATIN™ and/or ENDOSTATIN™ protein binding sites *in vivo* and *in vitro* to improve the understanding of angiogenesis-related protein influence, and thus also make possible the development of therapeutic agents for modifying angiogenesis related to disorders such as cancer and tumor development (see column 7, lines 3-8 and column 8, lines 40-43). Thus, while MacDonald does not explicitly state that one of the "other molecules or proteins" that label the binding peptides for use in detection and visualization techniques is a "fluorescing agent", visualization techniques involving attaching a fluorescent label, such as GFP, to a binding protein of interest are well-known and practiced in the art, and the skilled artisan would reasonably expect that such fluorescently-labeled peptides would be capable of performing their desired function. Accordingly, instant claims 4 and 5 are rendered obvious by the combined teachings of the above references.

Claim 3, as amended, is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/53804 by Smith et al. (published December 3, 1998), in view of Singh (*Curr Pharm Des*. 1999 Jun; 5(6):443-51).

Claim 3 is drawn to a composition comprising a peptide that contains the sequence HAIYPRH (SEQ ID NO: 1), wherein the peptide is fused to a chemotherapeutic agent, and the chemotherapeutic agent is methotrexate.

The teachings of Smith are discussed above. In particular, Smith teaches the compositions comprising the peptide HAIYPRH, and discloses that the peptide can be used to target genes, proteins, pharmaceuticals, or other compounds to particular muscle tissue by ligating the muscle-specific peptide to pharmaceuticals and chemotherapeutic agents (p. 10, lines 7-11). However, Smith does not teach the specific chemotherapeutic agent methotrexate.

Singh teaches the targeting and delivery of anticancer drugs, such as methotrexate (MTX) or adriamycin, to tumor cells by linking the drugs to a peptide ligand such as transferrin. Singh notes that the transferrin protein-chemotherapeutic agent conjugate was found to be effective both in vitro and in vivo against various tumor cell lines and human tumors (see abstract).

Because both Smith and Singh teach the use of peptide ligands to target specific tissues and ligation of these peptides to chemotherapeutic agents for treatment of cancer, it would have been *prima facie* obvious to one skilled in the art at the time the invention was made to use the specific chemotherapeutic agent methotrexate taught by Singh in the peptide composition taught by Smith. The skilled artisan would reasonably expect that the combination would be successful because Singh evidences that such peptide-chemotherapeutic agent conjugates are effective against tumor cells. Accordingly, the invention of instant claim 3 is rendered obvious in view of the combined teachings of the above references.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

EILEEN B. O'HARA
PRIMARY EXAMINER

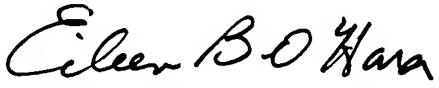
Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Ballard whose telephone number is 571-272-4479. The examiner can normally be reached on Monday-Friday 9AM - 5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kimberly Ballard, Ph.D.
August 12, 2007



EILEEN B. O'HARA
PRIMARY EXAMINER